UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: MAR 16 2012

SUBJECT: Science Review of Tolerance Petition 1F7920, Intended to Expand the Use of 1,4-Dimethylnaphthalene to Include Use on All Root and Tuber Vegetables (Crop Group 01) and Bulb Vegetables (Crop Group 03); Label Amendments for 67727-1, -3 and -4 Upon Tolerance Amendment Approval

Type of Data Review:	Human Health
Decision Number:	454569
DP Number:	396198
EPA File Symbol Number:	1F7920 (Tolerance), 67727-1, -3, -4 (Label Changes)
Chemical Class:	Biochemical
PC Code:	055802
Tolerance Exemption:	40 CFR 180.1142
MRID Nos.:	48590902 thru -07 (see "Note to RAL")

FROM: Gina M. Burnett, M.S., Biologist /s/
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Biopesticides & Pollution Prevention Division (7511P)

TO: Colin Walsh, M.S., Regulatory Action Leader
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ACTION REQUESTED

Technology Sciences Group, Inc., on behalf of 1,4Group, Inc., has submitted an application to amend the established exemption from the requirement of a tolerance for residues of 1,4-Dimethylnaphthalene (1,4-DMN). Currently, the tolerance exemption applies only to post-harvest use on potatoes. The submitted amendment seeks to include an exemption from the requirement of a tolerance when used on all root and tuber vegetables (EPA Crop Group 01) and all bulb vegetables (EPA Crop Group 03). The established tolerance exemption was supported by a full set of acceptable acute toxicity ("6-pack") data (MRIDs 43082510 thru -15), mutagenicity data (MRIDs43082416 thru -18, 46577001), and two residue studies conducted on potatoes (MRIDs 43266803 and 43594501). There is also a 90-day oral toxicity study (MRID 46316806) on file with the Agency. In support of the tolerance amendment, the applicant has submitted six new studies for review. These include: Dermal Sensitization using the Local Lymph Node Assay (LLNA) method (MRID 48590902), Prenatal Developmental Toxicity (MRID 48590903), Unscheduled DNA Synthesis (MRID 48590904), Skin Absorption (MRID 48590905), Reproduction and

Fertility Effects (MRID 48590906), and Carcinogenicity (MRID 48590907). The applicant has also submitted "Summary of the natural occurrence of 1,4-DMN in crops:" (MRID 48653101) and "GC/MS method for specific identification and confirmation of 1,4-DMN in plant material" (MRID 48653102).

RECOMMENDATIONS AND CONCLUSIONS

1. The current exemption from the requirement of a tolerance for 1,4,-DMN, listed at 40 CFR 180.1142, includes potatoes only (post harvest use to inhibit sprouting). An expansion to include the entire root and tuber vegetable crop group (EPA Crop Group 01) is ACCEPTABLE. Specifically, the residue data on file for potatoes may be bridged to all other vegetables in this crop group, as established by the Agency, if the use pattern remains the same.

2. An expansion of the exemption from the requirement of a tolerance for 1,4-DMN to include bulb vegetables (EPA Crop Group 03) is UNACCEPTABLE. The residue data on file for potatoes is not representative of the members of the bulb vegetable crop group and, as stated in the Agency's Oct 20, 2012, letter to the applicant, may not be bridged to support an exemption for this crop group. The applicant must address the following issues:
    a. What are the residues present on at least one member of the bulb vegetables crop group? (This may be determined by performing a guideline study or with rationale or modeling that is supported by legitimate data and/or information).
    b. How do these residues compare to the residues found on potatoes?
    c. How do these residues compare to the NOAEL levels established in the 90-day oral (MRID 46316806) and prenatal development (MRID 48590905) studies for 1,4-DMN?

3. Six toxicity studies were submitted in support of this action. Each is summarized below. The prenatal developmental study is a biochemical pesticide Tier I data requirement and is applicable to this action. The study is classified as ACCEPTABLE. Based on the findings from this study, the no-observed-adverse-effect level (NOAEL) of 1,4-DMN for maternal toxicity was 80 mg/kg/day, while the NOAEL for developmental toxicity was 250 mg/kg/day. The other five toxicity studies are also classified as ACCEPTABLE, but are not considered data requirements for this particular action.

4. Two studies were submitted containing information on the natural occurrence of 1,4-DMN in various crops. The Agency considers this information to be SUPPLEMENTAL; this information is insufficient to support an amendment of the tolerance exemption to cover bulb vegetables (EPA Crop Group 03).

Notes to RAL:

- For MRIDs 48590901 thru -06, there is a discrepancy between the file number in OPPIN/Documentum and what was hand-stamped on the first page of each document. For example, if you open MRID 48590901 in Documentum you see that the number 48590902 stamped on the hardcopy. In this review I refer to the hardcopy stamp number.
- Any label changes for EPA Reg No. 67727-1, -3, and -4 involving Conclusion 2 (above) are unacceptable.

DATA REVIEW

MRID 48590902: Unscheduled DNA Synthesis

The applicant has submitted a study measuring unscheduled DNA synthesis in the rat liver, following OCSPP Guideline 870.5550. The study concludes that 1,4-DMN has no genotoxic activity under the experimental conditions investigated.

CLASSIFICATION: The submitted study is ACCEPTABLE; however, this information was not required by the Agency for this particular action and does not change the Agency's conclusions regarding this action.

MRID 48590903: Skin Absorption

The applicant has submitted a study measuring *In vitro* precutaneous absorption of 1,4-DMN through human skin, following OCSPP Guideline 870.7600. The study found that the mean total dermal absorption of 1,4-DMN was 2.5 % of the dose applied.

CLASSIFICATION: The submitted study is ACCEPTABLE; however, this information was not required by the Agency for this particular action and does not change the Agency's conclusions regarding this action.

MRID 48590904: Dermal Sensitization

The applicant has submitted a dermal sensitization study utilizing the Local Lymph Node Assay (LLNA) method. The test substance did not induce contact hypersensitivity in mice after three epidermal induction exposures. The study concludes that 1,4-DMN is not a sensitizer.

CLASSIFICATION: The submitted study is ACCEPTABLE; however, this study does not fulfill any outstanding data requirements and is not required for the consideration of the requested action. There is already an acceptable dermal sensitization study on file for this chemical.

MRID 48590905: Prenatal Developmental Toxicity

The applicant has submitted a prenatal developmental study was conducted according to OCSPP Guideline 870.3700. In this study, 1,4-DMN was formulated in a vehicle of corn oil and administered by oral gavage at dose levels of 0 (vehicle control), 25, 80 or 250 mg/kg/day to female rabbits (23 per test group) over gestation days 6 through 28. Clinical observations, maternal body weight, body weight gain, and food consumption were monitored throughout gestation. All surviving animals were sacrificed on their respective 29th day of gestation and subjected to gross necropsy and cesarean section. No treatment-related clinical signs were noted during the study and gross necropsy findings were limited to those rabbits that underwent abortion. The gross necropsy findings consisted of changes in the gastrointestinal tract (dilatation of stomach and/or intestines) and were likely related to the lack of eating prior to/during the abortion (8 rabbits underwent abortion over days 20-27, with one resulting in maternal death).

Mean food consumption was significantly reduced in the 250 mg/kg/day treated does shortly after treatment initiation (over gestation days 6-9 and 9-12); this reduction in food consumption was likely treatment-related. Corollary reductions in mean body weight gain were observed in the 250 mg/kg/day treated group over gestation days 6-9. Alterations in uterus weight were not observed nor were changes seen in maternal body weight or body weight gain when corrected for uterus weight. As such, the changes seen early on in gestational body weight gain were considered to be solely associated with maternal toxicity.

Overall, no treatment-related differences in litter viability were detected. In addition, the number of male, female and total fetuses (sexes combined) was similar across the treated and control groups. Average fetal weights were unaffected by treatment. No structural alterations were evident from the fetal examinations (gross external, visceral, skeletal and cephalic), as such 1,4-DMN did not produce any frank malformations and was not teratogenic.

Therefore, based on the findings from this study, the no-observed-adverse-effect level (NOAEL) of 1,4-DMN for maternal toxicity was 80 mg/kg/day, while the NOAEL for developmental toxicity was 250 mg/kg/day.

CLASSIFICATION: The submitted study is ACCEPTABLE; additional prenatal developmental data is not required at this time.

MRID 48590906: Reproduction and Fertility Effects

The applicant has submitted an extended one-generation reproductive toxicity study measuring reproduction and fertility effects of 1,4-DMN in rats, following OCSPP Guideline 870.3800. In the study, 1,4-DMN was administered in the diet, at target concentrations of 0 (basal diet alone), 500, 2000 and 7500 ppm to Sprague-Dawley for the assessment of systemic, developmental and reproductive toxicity. Parental rats were fed the formulated diet for 2 weeks prior to mating, during the 2-week mating period, for up to 10 weeks for the parental males and through gestation, lactation and until scheduled necropsy for the parental females. F1 pups were exposed to 1,4-DMN during the lactation phase of the study and selected F1 offspring were exposed to the same concentration of the diet admixtures as the parental dams from rearing until scheduled sacrifice. P1 Litters (F1 offspring) were culled to 10 pups (5/sex), when feasible.

The study concludes that the NOAEL for systemic toxicity was 2000 ppm based on a single histological change in the kidney of one 7500 ppm treated rat. The NOAEL for developmental toxicity was also 2000 ppm based on delayed vaginal patency and preputial separation in the 7500 ppm group, although the delay in development was considered secondary to body weight effects that were attributed to reduced food consumption. The NOAEL for reproductive toxicity was 7500 ppm based on the lack of change in reproductive endpoints such as mating performance, fertility, fecundity, litter survival, sperm morphology/vaginal cytology as well as the lack of histological change in the reproductive organs.

CLASSIFICATION: The submitted study is ACCEPTABLE; however, this information was not required by the Agency for this particular action and does not change the Agency's conclusions regarding this action.

MRID 48590907: Carcinogenicity

The applicant has submitted a carcinogenicity study in rats following OCSPP Guideline 870.4300. In the study, 1,4-DMN was administered in the diet to Sprague-Dawley rats 7 days/week for a minimum of 52 weeks (chronic toxicity phase) or 104 weeks (carcinogenicity phase), at target concentrations of 0, 150, 500 and 3,750 ppm equivalent to target doses of 0, 10, 33 and 250 mg/kg/day. The study concludes that 1,4-DMN, under the conditions of this study, did not cause carcinogenicity.

CLASSIFICATION: The submitted study is ACCEPTABLE; however, this information was not required by the Agency for this particular action and does not change the Agency's conclusions regarding this action.

MRID 48653101: Summary of the natural occurrence of 1,4-DMN in crops

MRID 48653101 summarizes the current scientific literature on 1,4-DMN occurrence in crops. The applicant notes that 1,4-DMN has been detected in various crops including cocoa, coffee, apples, corn, raisins, tomatoes, apricot, peach, pear juice, eggplant, green peppers, star fruit, tea, radishes, oranges, cinnamon, poppies, and red beans. The applicant states that no information was available on the occurrence of 1,4-DMN in bulb crops.

CLASSIFICATION: The Agency considers this information to be SUPPLEMENTAL; this information is insufficient to support an amendment of the tolerance exemption to cover bulb vegetables (EPA Crop Group 03). Levels of naturally-occurring 1,4-DMN in plant matrices were not compared to residues that could be expected to occur in or on bulb vegetables following application of 1,4-DMN as a pesticide according to proposed label use directions.

MRID 48653102: GC/MS method for specific identification and confirmation of 1,4-DMN in plant material

In this study, various plant samples were extracted and analyzed by gas chromatography for 1,4-DMN. Detected 1,4-DMN was subsequently analyzed by mass spectrometry. The study does not present a list of all of the plant materials tested, only the ones where 1,4-DMN was detected. These include: radish, peach, cinnamon, and orange.

CLASSIFICATION: The Agency considers this information to be SUPPLEMENTAL; this information is insufficient to support an amendment of the tolerance exemption to cover bulb vegetables (EPA Crop Group 03). Levels of naturally-occurring 1,4-DMN in plant matrices were not compared to residues that could be expected to occur in or on bulb vegetables following application of 1,4-DMN as a pesticide according to proposed label use directions.

NO DERS WERE WRITTEN FOR THIS REVIEW

cc: G. Burnett, BPPD, C. Walsh, BPPD Science Review File, M. Xue/IHAD/ARS: MAR 16 2012